American Journal of Respiratory and Critical Care Medicine, 2026, 212(5), 893–896
https://doi.org/10.1093/ajrccm/aamag067
Published: February 21, 2026
Viewpoint: Turning the Air Blue

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Reconsidering resistance: a potentially overlooked risk factor for lung injury during assisted ventilation

Andrea Castellvi-Font[1,2,*] **and Ewan C. Goligher**[3,4,5,6]

[1]Department of Critical Care, Hospital del Mar, Hospital del Mar Research Institute (HMRI), Barcelona, Spain
[2]Department of Medicine and Life Sciences (MELIS), University Pompeu Fabra (UPF), Barcelona, Spain
[3]Department of Medicine, University of Toronto, Toronto, ON, Canada
[4]Toronto General Hospital Research Institute, Toronto, Canada
[5]Department of Physiology, University of Toronto, Toronto, Canada
[6]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
*Corresponding author: Andrea Castellvi-Font, MD, Critical Care Department, Hospital del Mar, Passeig Marítim de la Barceloneta, 25-29, Ciutat Vella, 08003 Barcelona, Spain (acastellvifont@hmar.cat).

The risk for ventilation-induced lung injury has traditionally been assessed in terms of static mechanics and elastic pressures. We contend that another component of the equation of motion may contribute to the progression of lung injury, particularly during assisted ventilation: inspiratory airway resistance.

Airway resistance (Raw) determines the pressure specifically generated by inspiratory flow (Raw = Δ*P*/Flow). However, as flow through the airways—particularly the endotracheal tube (ETT)—is often non-linear, resistance varies with flow and cannot be described by a single value. Flow may be laminar or turbulent: under laminar conditions, the flow profile is orderly, and pressure losses are proportional to flow, whereas turbulent flow is characterized by chaotic velocity patterns and disproportionate pressure losses (Figure 1). Transitional flow states between laminar and turbulent conditions are common in the respiratory system. Because flow decreases across successive airway generations, most inspiratory resistance is generated in central structures such as the ETT, upper airway, and main bronchi, while peripheral resistance becomes more relevant in obstructive diseases.[1-3]

Strategies to achieve lung-protective ventilation have focused almost exclusively on static mechanics such as elastance, plateau pressure, and driving pressure, under the assumption that these primarily determine ventilator-induced lung injury. We propose that elevated airway resistance may predispose to lung injury once patients transition to assisted ventilation with active respiratory muscle effort.

Airway resistance may contribute to progression of lung injury during spontaneous breathing

During passive ventilation, resistance is unlikely to contribute to lung injury progression. Pressures are generated entirely by the ventilator; increases in resistance may increase inspiratory pressures without contributing to lung stress. By contrast, during assisted ventilation, elevated resistance can amplify the consequences of high inspiratory effort while simultaneously increasing the effort required to generate flow—together predisposing to lung injury through interconnected mechanisms (Figure 2).

First, resistive loading combined with high respiratory drive and effort can generate markedly negative intrathoracic pressures, increasing venous return and left ventricular afterload, elevating pulmonary capillary pressures, and promoting negative pressure pulmonary edema.[4,5] Increased resistance and vigorous effort also generate large negative alveolar pressure swings, amplifying the transvascular gradient and promoting fluid leakage into the interstitial and alveolar spaces. In a crossover study by Bellani et al,[6] patients with matched tidal volumes and compliance exhibited more negative alveolar pressure as ventilatory support decreased and inspiratory effort increased, attributed to the pressure lost across the resistive load, mainly the ETT and narrowed airways. In preclinical models, sustained resistive breathing leads to non-cardiogenic pulmonary edema through both inflammatory and mechanical pathways.[7]

Third, increased inspiratory resistance promotes the development of pendelluft from inspiratory effort, resulting in excess regional stress and strain, particularly in heterogeneous lung injury.[8,9] In an experimental ARDS model, Pellegrini et al[10] showed that pendelluft occurred exclusively during spontaneous breathing and was significantly exacerbated by increased resistance via ETT narrowing. Similarly, Bassi et al[11] demonstrated that in acute hypoxemic respiratory failure, the correlation between inspiratory effort and pendelluft strengthened when resistance exceeded 5 cm H_2O/L/s. Thus, resistance not only increases effort but also channels it into potentially injurious regional mechanics.

Received: July 31, 2025. **Accepted:** December 25, 2025

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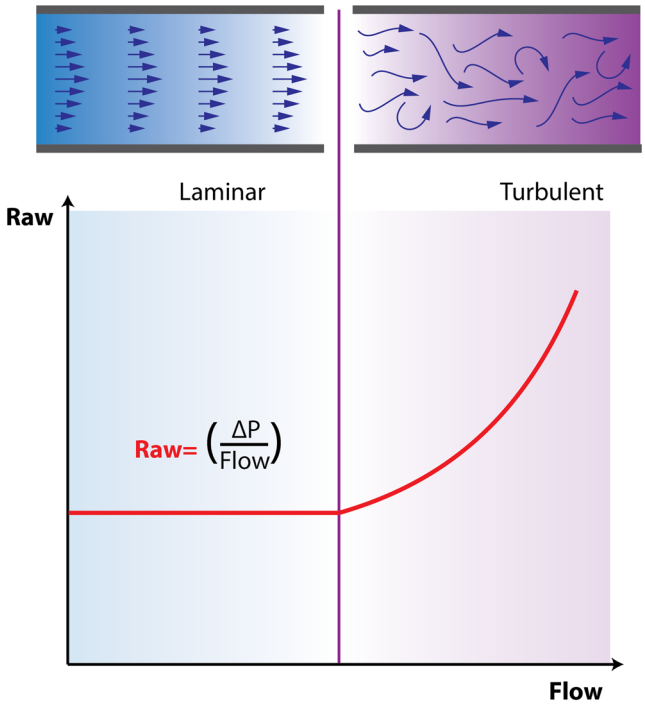

Figure 1 Pressure–flow relationships in laminar and turbulent flow. Schematic representation of laminar versus turbulent flow and their implications for the pressure–flow relationship. In laminar flow, pressure increases linearly with flow, and resistance (raw = ΔP/flow) remains constant. In contrast, turbulent flow introduces a non-linear relationship, where small increases in flow result in larger increases in pressure. In mechanically ventilated patients, flow is almost never purely laminar—turbulence is nearly always present to some degree, especially in the presence of airway narrowing due to endotracheal tube obstruction (eg, secretions, biofilm, blood), bronchial inflammation, or bronchospasm. This complicates the estimation of inspiratory resistance and underscores the need to interpret raw values in the context of the prevailing flow regime.

Challenges to accounting for inspiratory resistance in clinical practice

Two main challenges make it difficult to integrate resistance as a target for lung-protective ventilation: measuring it and modifying it.

Assessing resistance during assisted ventilation at the bedside remains difficult. Modern ventilators estimate resistance using the Least Squares Fit (LSF) method, which fits pressure, flow, and volume waveforms in real time.[12] However, when spontaneous effort is present, the LSF requires accounting for inspiratory muscle pressure (Pmus)—typically via esophageal pressure monitoring—to maintain accuracy. Without adjusting for Pmus, LSF may underestimate resistance and overestimate compliance.[13]

Because the injurious effects of resistance depend on elevated respiratory effort, resistance-related risk may be inferred by monitoring effort itself. Occlusion pressure (Pocc) as described by Bertoni et al,[14] offers a non-invasive surrogate. Elevated Pocc has been associated with more negative alveolar pressures, increased pendelluft,[15] and worse outcomes.[16] Incorporating Pocc into routine monitoring may therefore help identify patients at risk of injurious breathing mechanics.

The second challenge is intervening. Strategies include reducing resistance and controlling respiratory effort—which may be particularly beneficial when resistance is high.

To reduce resistance, simple interventions include optimizing ETT size, promoting secretion clearance, considering early tracheostomy, and avoiding inspiratory flow starvation in volume-cycled ventilation. While higher inspiratory flows increase resistive pressure, they may reduce patient effort and attenuate excessive negative alveolar pressure swings when flow delivery better matches patient demand. Pharmacologic therapies such as bronchodilators and mucolytics—though traditionally used in obstructive disease—may benefit ARDS patients with elevated airway resistance. Early physiologic studies have shown that resistance is increased even in restrictive injury patterns such as ARDS,[1,17] suggesting it may serve as both a marker of severity and a potential therapeutic target.

Controlling respiratory effort may mitigate the harmful effects of high resistance. This can be achieved through carefully titrated sedation, partial neuromuscular blockade, or extracorporeal CO_2 removal. Adjusting PEEP, FiO_2, and pressure support may also help modulate effort, and non-mechanical factors such as pain and agitation should be routinely assessed and managed.

Summary

Inspiratory airway resistance may represent a clinically relevant and underappreciated contributor to lung injury progression during assisted ventilation. Elevated resistance can increase inspiratory effort, distort regional mechanics, and exacerbate pulmonary edema. While respiratory elastance during controlled ventilation is gaining traction as a marker of lung injury risk,[18,19] airway resistance merits further attention during the assisted phase.

The relative contributions of artificial airways, natural upper airway structures, and disease-related changes to total resistance remain uncertain. Airway closure may increase resistance and cause expiratory flow limitations, but this phenomenon remains poorly characterized in the context of assisted ventilation.

Moving forward, we need accurate, real-time tools to monitor resistance in the context of assisted ventilation to guide individualized management. Attention to resistance and—particularly—flow-resistive pressure may prove critical to protecting the lung during the transition from controlled to assisted ventilation.

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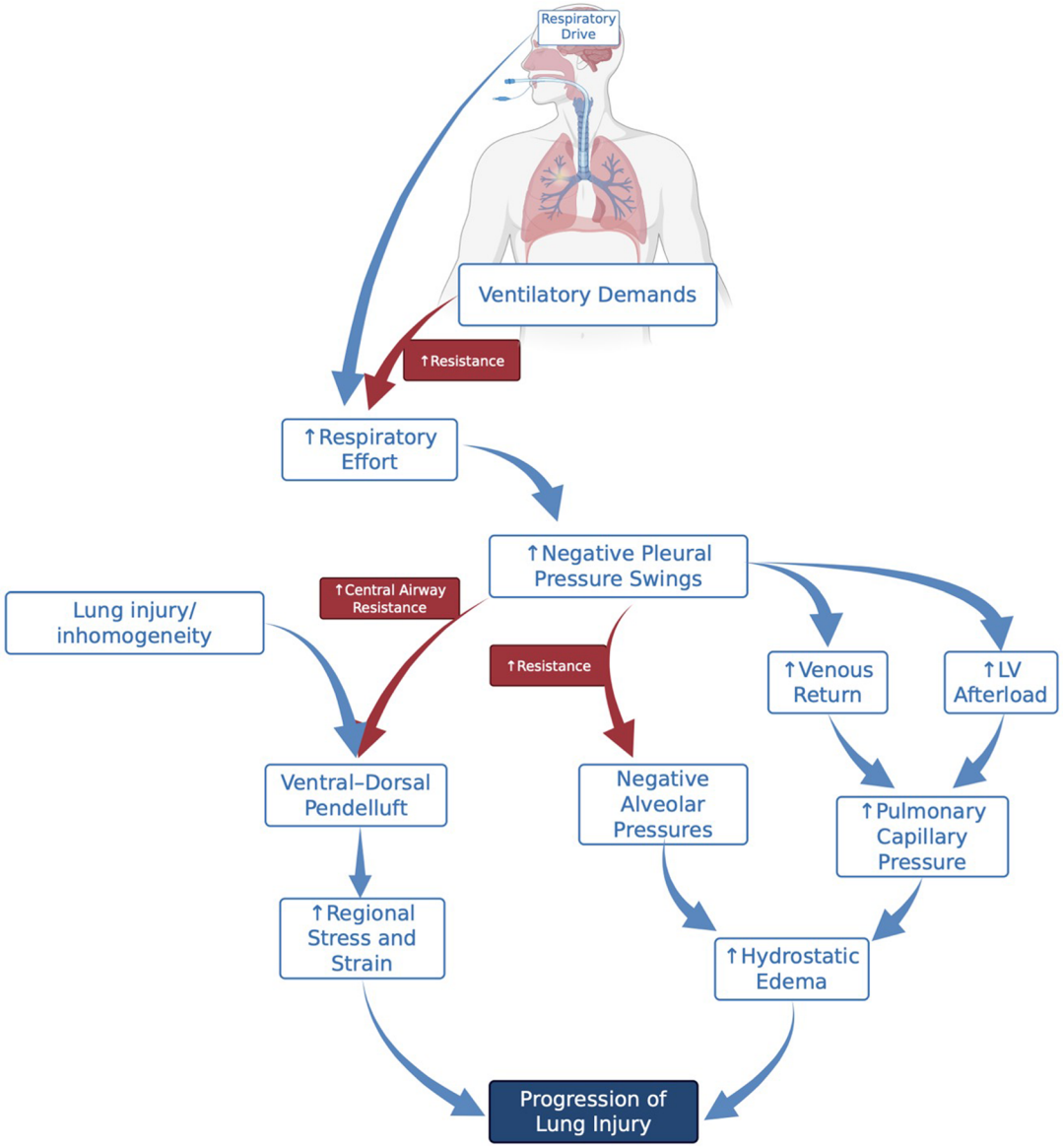

Figure 2 Conceptual model of lung injury mechanisms amplified by elevated inspiratory airway resistance. Elevated inspiratory airway resistance increases the muscular effort required to generate flow and enhances pleural and alveolar pressure swings, thereby promoting negative pressure–related injury and hydrostatic edema. It also contributes to pendelluft and regional stress and strain, particularly in heterogeneous lungs. The red arrows highlight points where high resistance amplifies these injurious pathways, ultimately converging toward the progression of lung injury during assisted ventilation. *All these mechanisms are initiated by the presence of an active respiratory drive*.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material.

Funding

Dr Goligher is supported by an Early Career Investigator award from the National Sanitarium association.

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